Highlights on Pharmacogenetics and Pharmacogenomics in Depression

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1.1 Introduction

As molecular biology became more and more integrated in all medical fields, in the previous century, genetic polymorphisms were demonstrated to contribute to the pathogenesis of major psychiatric disorders such as mood disorders and schizophrenia (Bertelsen 1985). The following step was to demonstrate that also response to treatments such as antidepressant drugs frequently clusters in families since it has a genetic component. It was estimated that genetics accounts for 20–95% of variability in CNS (central nervous system) drug disposition and pharmacodynamics (Cacabelos et al. 2012).

Since these findings, genetics and pharmacogenetics have been considered a powerful tool to develop objective diagnostic markers and provide guidance for tailored treatments in psychiatry. Response to psychotropic drugs shows high variability among individuals, and currently the lack of validated biomarkers of treatment outcomes results in the use of a trial and error principle to identify the most effective and tolerated treatment. This increases the time needed to reach symptom remission or in some cases does not allow remission, with possible evolution in a chronic disease. The prevalence, personal, and social burned of psychiatric disorders stimulated a strong wave of research aimed to identify biomarkers able to personalize treatments in a reproducible and valid way.

Among mental disorders, depressive disorders are responsible for highest burden in terms of disability-adjusted life years (DALYs) (40.5%) (Whiteford et al. 2013) and consequently for the highest health expenditure (direct costs alone amount to 42 billion dollars per year in Europe (Sobocki et al. 2006)). About one third of patients with MDD (major depressive disorder) reaches complete symptom remission after the first antidepressant trial, and about two thirds meets the criteria for treatment-resistant depression (i.e., inadequate response to two or more treatments) (Trivedi and Daly 2008). Since the availability of antidepressants belonging to different classes (i.e., with different mechanisms of action) and non-pharmacological treatments (e.g., psychotherapy) that can be prescribed alone or in combination, the lack of treatment targeting is responsible for part of the unsuccessful outcomes. Biomarkers and particularly genetic polymorphisms have been considered excellent candidates to provide treatment targeted on the individual patient in the last three decades. Human genomes differ for millions of polymorphisms, the most common of which are single nucleotide polymorphisms (SNPs), i.e., replacement of a single DNA base. Less common and

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Y.-K. Kim (ed.), *Understanding Depression*, https://doi.org/10.1007/978-981-10-6580-4_1

larger variations include deletions, insertions, and copy number variations, but genetic studies of complex traits (such as drug response) are usually focused on SNPs.

After the first enthusiastic findings in the 1990s that involved some candidate genes such as the serotonin transporter (see Sect. 1.2.1 for details), the lack of consistent replication in the following studies resulted in a period of uncertainty and disappointment without the possibility to develop any clinical application. In the meantime, advances in genotyping technologies and analysis approaches have been exponential and made possible a new wave of innovation and progress in the last 10 years. Particularly, genome-wide arrays (a technology that allows the genotyping of 500 K–3 million polymorphisms throughout the whole genome) became more and more available in terms of costs, and innovative statistical approaches have been developed, thanks to the generation and growth of genome-wide databases. Indeed, the pharmacogenomics of antidepressants is today known to be a complex trait, i.e., the result of the effect of multiple genetic loci that may have additive or multiplicative effect. Recent approaches have tried to take into account this complexity by using multilocus models that include hundreds or thousands variants at the same time. In the following sections these recent methodologies and their results are described, but first of all candidate gene studies—that were the starting point of antidepressant pharmacogenetics—are briefly summarized.

1.2 Pharmacogenetics of Antidepressants: Are Candidate Gene Studies Useful?

The term "pharmacogenetics" was coined when the first studies that investigated variants possibly associated with drug response were published. Those studies were based on the hypothesis that a small number of polymorphisms in some genes could be responsible for the most part of variance in treatment outcome. Since this was shown not to be the case, the usefulness of this type of study could be considered doubtful. The following sections discuss this issue taking into account previous findings and clinical applications of candidate gene studies.

1.2.1 Main Findings of Candidate Gene Studies

Candidate gene studies are focused on a limited number of polymorphisms in genes which products are known to be involved in drug metabolism (pharmacokinetics) or drug mechanisms of action (pharmacodynamics). The most studied and confirmed genes in the former group are cytochrome P450 (CYP450) genes that are responsible for antidepressant metabolism in the liver and ABCB1, encoding for the P-glycoprotein that is responsible for drug transport through the blood brain barrier (BBB). In the latter group, the serotonin transporter (SLC6A4), serotonin receptors, brain-derived neurotrophic factor (BDNF), and genes related to signal transduction (particularly GNB3 and FKBP5) were the most replicated for association with antidepressant response (Fabbri et al. 2016).

CYP450 genes are highly polymorphic resulting in several groups with different metabolizing activity (from poor metabolizers to ultra-rapid metabolizers, with extensive metabolizers being the group with the normal activity level). CYP2D6 and CYP2C19 isoforms were the most studied as modulators of antidepressant treatment outcomes (both in terms of efficacy and side effects). There is convincing evidence that functional polymorphisms in these CYP450 genes affect plasma levels of target antidepressants and their metabolites, but findings are more contradictory for clinical outcomes. In the latter group, the most replicated result was higher occurrence/severity of side effects in non-extensive CYP2D6 or CYP2C19 metabolizers (Müller et al. 2013). An explanation of these findings may be a non-linear relationship between antidepressant plasma levels and efficacy/side effects that was not possible to clearly define probably because of small sample size of previous studies. Poor

metabolizers are indeed the group that is expected to show the most extreme clinical outcomes, but it is also the rarest group (around 1.5–3% in the Caucasian population), and most part of available studies was performed in samples including few hundreds of subjects or less (Porcelli et al. 2011). A meta-analysis investigating CYP2D6 and CYP2C19 association with antidepressant efficacy and side effects is still lacking, and it would be very helpful in clarifying the value of pharmacogenetic tests including these CYP450 genes in their predictive model (see Sect. 1.2.2).

CYP450 phenotypes affect antidepressant plasma levels, while P-glycoprotein (ABCB1 gene) limits the uptake of many antidepressants into the brain. Some polymorphisms in this gene (rs2032582, rs1045642, rs2032583, rs2235015) were associated with altered P-glycoprotein expression and/or function and with antidepressant efficacy (Fabbri et al. 2016). The distinction between antidepressants that are or not targets of P-glycoprotein and the affinity of P-glycoprotein to each target antidepressant is relevant in this case and was not always considered by pharmacogenetic studies.

Among genes responsible for antidepressant pharmacodynamics, some polymorphisms of the SLC6A4 gene are included in all the pharmacogenetic tests available on the market (see Sect. 1.2.2). SLC6A4 codes for the serotonin transporter that is the main target of the most part of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). In particular, the 5-HTTLPR insertion-deletion variant was investigated by more than 50 studies despite the mean sample size was limited considering current standards (around 150 subjects). The last meta-analysis suggested that the polymorphism is associated with treatment efficacy particularly in some groups (Caucasian subjects treated with SSRIs) (Porcelli et al. 2012), despite the effect size of this variant alone is estimated to be modest (odds ratio between 1.53 and 2.10).

Among serotonin receptors, HTR2A (serotonin receptor 2A) may be pivotal for the final antidepressant effect since it mediates the increase in the firing rate of serotonergic neurons and hippocampal plasticity in animal models (Qesseveur et al. 2016). The effect of rs6313 and rs7997012 on antidepressant efficacy was confirmed at meta-analytic level (odds ratio between 1.33 and 1.92) despite inconsistent findings were reported by individual studies (Lin et al. 2014).

BDNF was the most studied among genes coding for neurotrophins, a family of proteins that control the survival, development, and function of neurons. BDNF is hypothesized to serve as link between antidepressant drugs and the neuroplastic changes that result in the improvement of depressive symptoms. The Valine66Methionine (Val66Met or rs6265) is a BDNF functional polymorphism since the Met allele results in decreased levels of active BDNF in vitro and it may be associated with psychiatric disorders including mood disorders and anxiety (Glatt and Lee 2016). In depressed patients, the cumulative evidence is partially inconsistent with these observations since the heterozygote genotype (Met/Val) was reported to have higher chances of treatment response and remission even if the effect size was again small (odds ratio between 1.26 and 1.74) (Niitsu et al. 2013). This finding may be interpreted as the result of a complex pattern of molecular and behavioral consequences of BDNF levels in different brain areas. For example, higher BDNF levels in the hippocampus were associated with antidepressant effects, but BDNF actions might be different or even opposite in different brain regions. The best example is the ventral tegmental area-nucleus accumbens (NAc) dopaminergic reward circuit, in which chronic stress increases BDNF expression (Yu and Chen 2011). Another relevant issue to consider is the interaction between neurotrophins and glucocorticoids that affects depressive symptoms and antidepressant response. FKBP5 (FK506-binding protein 52) increases the sensitivity of the glucocorticoid receptor (GR) and plays a role in stress response and depressive states. Drugs that reduce FKBP5 gene expression were demonstrated to elicit increase of BDNF levels and antidepressant effects (Xing et al. 2015). rs1360780 has been the most studied polymorphism because carriers of the TT genotype showed FKBP5 levels that were twice as high as C allele carriers in vitro (Binder

et al. 2004). Meta-analytic results confirmed a small advantage of T allele carriers in a stratified analysis of patients of European origin (Niitsu et al. 2013) and the polymorphisms was included in some of the pharmacogenetic tests available on the market (see Sect. 1.2.2).

Another pivotal molecule in signal transduction is the guanine nucleotide-binding protein (G protein) that mediates a broad range of signaling cascades in response to a number of hormones and neurotransmitters. GNB3 encodes for the beta polypeptide 3 of that protein, and the rs5443 (C825T) polymorphism was object of particular interest since the T allele leads to altered activity of the protein (Ruiz-Velasco and Ikeda 2003). The cumulative evidence from pharmacogenetic studies suggests better response in T allele carriers especially in subjects of Asian ancestry despite controversial results were reported (Niitsu et al. 2013).

A number of other candidate genes have been investigated in addition to the ones discussed in this section, particularly other genes which products are involved in mechanisms of antidepressant action such as HTR1A (serotonin receptor 1A), HTR2C (serotonin receptor 2C), COMT (catechol-O-methyltransferase), MAOA (monoamine oxidase A), tryptophan hydroxylase 1 (TPH1), glutamatergic receptors, proteins involved in BDNF signaling or other neurotrophins, and interleukins (Fabbri et al. 2013).

Despite the effect sizes of individual polymorphisms are small as discussed in this section and the candidate gene approach is clearly limited since the complexity of the mechanisms involved in antidepressant response, we suggest that the study of the pharmacogenetics of antidepressants should not be separated by the understanding of the biological mechanisms through which genes affect the phenotype. A hypothesis-free approach (analysis based on genome-wide data) is a powerful tool for exploration, but meaningful clinical applications are unlikely without the clarification of the contribution of individual genes in terms of biological role. Indeed, all the studied clinical applications are currently based on the results of candidate gene studies.

1.2.2 Clinical Applications

The pharmacogenetic tests currently available on the market are based on different combinations of polymorphisms in candidate genes that usually include those discussed in Sect. 1.2.1, particularly SLC6A4, HTR2A, CYP450 genes, and ABCB1. These tests are quite popular, thanks to the Web, and patients may decide by themselves to undergo the test and bring the results to their psychiatrist for interpretation and prescription of the "right" drug. According to the published data of the companies that commercialize these tests, antidepressant treatment guided by genotyping according to their algorithm may improve symptom remission (Hall-Flavin et al. 2013; Singh 2015) and reduce health-care utilization (Winner et al. 2013) and costs compared to treatment as usual (Winner et al. 2015). The main concern is the unavailability of the treatment decision algorithm based on the polymorphisms included in each of these tests, thus replication by independent investigators that do not collaborate with these companies was not performed. A couple of academic studies had similar designs and compared treatment guided by genotype versus treatment as usual, but they took into account polymorphisms in single candidate genes. They suggested that rs2032583 and rs2235015 polymorphisms in the ABCB1 gene may be useful to guide dose adjustments or drug switch (Breitenstein et al. 2014), and genotyping of FKBP5 rs1360780 may improve treatment outcome compared to treatment as usual (Stamm et al. 2016). The cost-effectiveness of these tests is still unclear.

1.3 Pharmacogenomics of Antidepressants

The cost of genotyping has shown more than an exponential decrease in the last decades, and at the same time, genotyping technologies became better and better. According to the US National Human Genome Research Institute (NHGRI), the reductions in DNA sequencing cost exceeded

the Moore's Law (which describes a long-term trend in the computer hardware industry that involves the doubling of "compute power" every 2 years) around 2008, indicating more than excellent technology improvements in the field (https://www.genome.gov/sequencingcostsdata/). Thus, the new standard approach of research became genomics or pharmacogenomics that consists in the study of polymorphisms throughout the whole genome using genome-wide arrays or sequencing.

1.3.1 Genome-Wide Association Studies (GWAS)

Genome-wide arrays allow the genotyping of 300 K–3 millions of common polymorphisms (mainly SNPs) throughout the whole genome, and they are designed to capture especially tag polymorphisms (i.e., polymorphisms that are inherited in conjunction with other polymorphisms), validated polymorphisms, and possibly polymorphisms in functional areas of the genome or in groups of genes that are hypothesized to be relevant for a particular type of study. The genome-wide technology provides high-throughput multiplex processing of samples at reasonable costs and overcomes the need of any a priori hypothesis that represented one of the limitations of candidate gene studies. At least ten GWAS of antidepressant response/side effects have been performed at the time this chapter was written (Uher et al. 2010; Garriock et al. 2010; Ising et al. 2009; Myung et al. 2015; Biernacka et al. 2015; Sasayama et al. 2013; Tansey et al. 2012; Cocchi et al. 2016; Li et al. 2016; Ji et al. 2013) in addition to meta-analyses (GENDEP Investigators, MARS Investigators, and STAR*D Investigators 2013), but no genome-wide convincing result has been reported. The usually accepted genome-wide threshold for significance is 5×10^{-8} since hundreds of thousands of tests are performed by GWAS, and this requires correction for multiple testing.

In samples that were of main Caucasian origin, the best findings were some intergenic SNPs on chromosome 1 (rs2136093, rs6701608, rs2136094) and 10 (rs16920624, rs11598854, rs7081156) (Uher et al. 2010) and SNPs in the UBE3C (rs6966038), BMP7 (rs6127921) and RORA (rs809736) genes (Garriock et al. 2010), RFK (rs11144870), GRK5 (rs915120) (Ji et al. 2013), and rs6989467 in the 5′ flanking region of the CDH17 gene (Ising et al. 2009). The GWAS in the largest Caucasian sample identified one significant variant (the intergenic SNP rs1908557) (Li et al. 2016). In Asian samples, a couple of genome-wide significant SNPs were reported in the AUTS2 gene (rs7785360 and rs12698828) that has been implicated in neurodevelopmental disorders including autism but also schizoaffective and bipolar affective disorders (Myung et al. 2015). This study was carried out in sample of Korean origin, but another GWAS in an independent sample of the same ethnic origin reported different findings that involved the CTNNA3 gene and inorganic cation transmembrane transporter activity pathway (Cocchi et al. 2016). The GWAS on the largest Asian sample (mainly Chinese subjects) did not report any genome-wide significant result, but some SNPs were close to significance in the meta-analysis of this data with a Caucasian sample (in the HPRTP4 pseudogene/VSTM5 region), and one suggestive finding was reported in the 5′ upstream of the NRG1 gene (neuregulin-1 that is involved in brain development and it was associated with mental disorders, particularly schizophrenia) (Biernacka et al. 2015). The last Asian GWAS was performed in a quite small Japanese sample, and it reported nonsignificant signals in the CUX1 gene (rs365836 and rs201522) (Sasayama et al. 2013).

An overview of GWAS results and functions of the genes involved by the top findings is reported in Table 1.1.

This list of non-replicated results may look disappointing and difficult to interpret since GWAS were expected to represent a turning point in antidepressant pharmacogenomics. Different issues are hypothesized to be responsible for the paucity of genome-wide findings and the lack of result replication. In detail, (1) the samples of previous GWAS included hundreds of subjects or

Table 1.1 Summary of genome-wide association studies (GWAS) results

Study	Sample size	Ethnicity	AD	Top results (p value)	Biological role
Ising et al. (2009)	339 + 361 for replication	Caucasian	Mixed ADs	rs6989467 in the 5′ flaking region of CDH17 ($p = 7.6 \times 10^{-7}$)	CDH17 (cadherin 17) codes for a calcium-dependent, membrane-associated glycoprotein that is not expressed in the CNS, a connection to antidepressant response is difficult to hypothesize
Uher et al. (2010)	706	Caucasian	Escitalopram Nortriptyline	rs2136093 (3.82×10^{-7}), rs6701608 (4.66×10^{-7}), rs2136094 (5.86×10^{-7}), s16920624 (7.37×10^{-7}), rs11598854 (7.67×10^{-7}), rs7081156 (1.01×10^{-6})	Intergenic SNPs, a mechanism for involvement in antidepressant effect is difficult to hypothesize
Garriock et al. (2010)	1491	Mainly Caucasian	Citalopram	rs6966038 in UBE3C (4.65×10^{-7}), rs6127921 100 Kbp from BMP7 (3.45×10^{-6}), rs809736 in RORA (8.19×10^{-6})	UBE3C codes for an ubiquitin protein ligase that is expressed in the CNS including prefrontal cortex and hippocampus, specific mechanisms linking it to antidepressant action are unknown. BMP7 codes for bone morphogenetic protein 7 that acts as a secreted ligand of the TGF-beta and it is expressed in the CNS. RORA codes for a member of the NR1 subfamily of nuclear hormone receptors that regulates the expression of some genes involved in circadian rhythm
Ji et al. (2013)	499	Caucasian	Escitalopram Citalopram	rs11144870 in RFK (1.04×10^{-6}), rs915120 in GRK5 (1.15×10^{-5})	RFK codes for an enzyme that catalyzes a critical step of vitamin B2 metabolism. B vitamins were suggested to affect the risk of depressive symptoms (Ji et al. 2013). GRK5 codes for a member of the G protein-coupled receptor kinase subfamily that regulates monoamine receptors such as β1-adrenergic receptor and dopamine D1A receptor (Ji et al. 2013)
Li et al. (2016)	4536	Caucasian	Bupropion	rs1908557 (2.6×10^{-8})	Intergenic SNP within the intron of human spliced expressed sequence tags in chromosome 4

Study	Sample size	Ethnicity	AD	Top results (p value)	Biological role
Myung et al. (2015)	870	Korean	Mixed SSRIs	rs7785360 and rs12698828 in AUTS2 (3.57×10^{-8})	AUTS2 (autism susceptibility candidate 2) has been implicated in neurodevelopment and as a candidate gene for several neuropsychiatric disorders including autism, schizoaffective, and bipolar affective disorders (Myung et al. 2015)
Biernacka et al. (2015)	865	Mainly Chinese	Mixed SSRIs	rs56058016 in VWA5B1 (1.1×10^{-7}), rs4747621 (1.75×10^{-7}), rs7041589 (5.40×10^{-7}), rs113243734 in ZC3HAV1L (5.64×10^{-7}), rs9328202 in RPS25P7 (6.15×10^{-7})	VWA5B1 codes for von Willebrand factor A domain containing 5B1 that is a large multimeric glycoprotein found in blood plasma but expressed also in some brain areas (particularly hypothalamus), but a biological mechanism of connection to antidepressant response is difficult to hypothesize ZC3HAV1L encodes for a protein of unclear function that is lowly expressed in the CNS. RPS25P7 is a pseudogene
Sasayama et al. (2013)	92 + 136 for replication	Japanese	Mixed	rs365836 and rs201522 in CUX1 (2.3×10^{-6} and 4.0×10^{-6}, respectively)	CUX1 (cut-like homeobox 1) codes for a domain of a DNA-binding protein that may regulate gene expression, morphogenesis, differentiation, and cell cycle progression. It may be implicated in disrupt cognition, social behavior, and autism (Doan et al. 2016; Liu et al. 2016)

Only results referred to individual polymorphisms are reported in this table and not findings of multi-marker analyses. For two GWAS (Tansey et al. 2012 ; Cocchi et al. 2016) no relevant top findings were reported in the SNP level analysis. Biological role refers to the function of the coded protein and the putative biological mechanism by which it may be relevant to antidepressant effect. Gene expression in the CNS was checked using GTEx Consortium data (http://www.gtexportal.org/home/). Genome-wide significant findings were underlined. *ADs* antidepressants, *CNS* central nervous system, *SSRIs* selective serotonin reuptake inhibitors

few thousands at maximum, while samples of tens of thousands are probably needed to identify associations with common polymorphisms having small effects (odds ratio of the best GWAS findings are usually 1.1–1.2); (2) very limited covering of genomic polymorphisms were provided by previous GWAS that included around 1 million SNPs or less in most part of cases, while around 40 million of SNPs were mapped in the human genome according to recent data (McCarthy et al. 2016); (3) antidepressant response is known to be a polygenic trait, and statistical tests based on individual polymorphisms are expected to provide less power compared to multi-marker tests (see Sect. 1.3.2), but previous GWAS have been mostly focused on individual polymorphisms.

Taking into account the reported limitations of available GWAS of antidepressant response, there are two main possible strategies to improve them

(in addition to provide better covering of genome variants): recruit new larger MDD samples characterized for antidepressant response and/or develop analysis approaches to maximize the power of detecting associations in the available samples. Some examples of the latter are provided by multi-marker tests discussed in Sect. 1.3.3.

1.3.2 Sequencing Studies

As reported at the beginning of Sect. 1.3, the cost of sequencing dropped down more than exponentially in the last 15 years. In 2001 the first draft of the human sequence was published, thanks to the Human Genome Project (HGP), one of the world's largest collaborative biological projects (International Human Genome Sequencing Consortium 2004). The HGP had a cost of about 2.7 billion dollars; now the cost of sequencing is about 1.000 dollars per genome providing the benchmark for routine, affordable personal genome sequencing.

Unfortunately, only one sequencing study focused on the genomics of antidepressant response and only exons (the coding segments of the genome) were sequenced. rs41271330 in the bone morphogenetic protein (BMP5) gene was found as promising marker of response by this study (Tammiste et al. 2013), suggesting a link with one of the top findings of a previous GWAS (rs6127921 in the BMP7 gene (Garriock et al. 2010)). Another study was limited to a functional exome array, and it revealed an exome-wide significant finding in a methylated DNA immunoprecipitation sequencing site. It also reported that a combination of this and other two exome variants predicted antidepressant response with area under the receiver operating characteristic (ROC) curve of 0.95 (Wong et al. 2014). This study was performed in a Mexican-American sample, and the attempt to replicate the three-locus model in three Caucasian GWAS failed (Uher et al. 2015); thus the result could be interpreted as highly influenced by ethnicity or other specific characteristics of the sample or as a false positive.

The generation of sequencing data is growing fast, and it is expected to accelerate in the next few years, also in the context of a number of national projects involving the creation of biobanks (e.g., the US Precision Medicine Initiative; see https://www.nih.gov/research-training/allofus-research-program). Thus, the use of sequencing data is expected to become the standard genomic data used for all genomic and pharmacogenomic studies in the relatively near future. Sequencing allows the identification of rare variants that are not included in GWAS arrays and the application of multi-marker tests that is based on the burden of rare variants in a specific gene or pathway of the genome.

1.3.3 Multi-Marker Tests Based on Whole Genome Data

The generation of genome-wide data and more recently sequencing data provided the opportunity to develop analysis approaches that combine the effect of a number of variants at the same time. This type of approach started from taking into account that the functional units of the genome can be identified in genes and that genes can be grouped according to the biological processes their products play a role in. The latter is called pathway analysis, and it consists of the analysis of all the polymorphisms in the genes that are part of the same biological pathway. This method is expected to reduce the confounding effects of heterogeneity within and across samples (i.e., heterogeneity is expected to impact more on individual polymorphisms than pathways), thus increasing power and chances to replicate findings in independent samples. Available pathway analysis supported the involvement of neuroplasticity and inflammation pathways in antidepressant response (Uher et al. 2015; Ising et al. 2009; Fabbri et al. 2014; Fabbri et al. 2015; O'Dushlaine et al. 2014; Hunter et al. 2013; Cocchi et al. 2016). Particularly, the long-term potentiation (LTP) pathway (Hunter et al. 2013), the inorganic cation transmembrane transporter activity pathway (Cocchi et al. 2016), and the GAP43 pathway (Fabbri et al. 2015) are involved in hippocampal plasticity and neurogenesis that are mechanisms known to mediate the antidepressant effect (Tanti and Belzung 2013). These

pathways included a number of genes coding for glutamate receptors (GRM1, GRM5, GRIA1, GRIN2A, GRIN2B, GRIN2C), postsynaptic L-type voltage-dependent Ca2+ channels (CACNA1C, CACNA1C, CACNB1, CACNB2), regulators of GABA and glutamatergic neurotransmission (e.g., ZDHHC7, NRG1, and HOMER1), and cell adhesion processes (e.g., FN1, EFNA5, and EPHA5). Abnormalities in inflammatory cytokine production and immune cell activation represent another key pathogenetic process in MDD, and antidepressants were demonstrated to restore these abnormalities. In particular the KEGG B cell receptor signaling pathway (Fabbri et al. 2014), the antigen processing and presentation pathway, and the tumor necrosis factor pathway (Hunter et al. 2013) were suggested to affect antidepressant response. Finally, genes involved in extracellular matrix remodeling (e.g., ADAMTSL1, CD36, PON2, APOB, and PIK3R1) and thus modulating the release of inflammatory factors were associated with antidepressant efficacy (Ising et al. 2009).

Polygenic risk scores (PRS) are another relatively recent multi-marker approach that was developed to analyze genome-wide data. PRS capture in a single variable the additive effect of SNP alleles across the whole genome. In contrast to the analysis of single SNPs (that requires stringent level of statistical significance), PRS are constructed from multiple SNPs with lower evidence of association, with the assumption that genetic markers that do not meet the genome-wide significance threshold might have good predictive power when they are considered collectively. The typical approach of studies using PRS is to estimate the polygenic score in a training sample and then test it in a validation or target sample in order to replicate the predictive value of the PRS. Unfortunately, the available studies investigating antidepressant response showed very unsatisfying or absent predictive value of PRS across independent samples. The best finding suggested that a PRS associated with symptom remission may account for approximately 1.2% of the variance in remission in the validation sample (GENDEP Investigators, MARS Investigators, and STAR*D Investigators 2013) that was statistically significant but clearly not enough for future translation in any possible clinical application. The PRS approach was a recent attempt to overcome the limitations of single marker analysis and move toward the identification of the complex polygenic contribution of polymorphisms to antidepressant response, but we suggest that it still needs methodological improvements. This observation is based on the fact that PRS had results below the expectations also for traits with a demonstrated high genetic contribution such as schizophrenia, since twin studies suggested heritability around 80% and PRS were able to explain 1.4–4.7% of phenotype variance in case-control samples (Derks et al. 2012). Some of the issues limiting the potential of PRS may be the use of broad clinical definitions or diagnosis for heterogeneous traits and the use of addictive models of the SNPs included in the score that could be an oversimplification of the reality (other types of interactions are possible such as multiplicative). Further, as stated above, not all variants are covered in present PRS studies.

To conclude this section, more sophisticated statistical methods are expected to be used in the future. An example is the application of approaches based on machine learning to antidepressant pharmacogenomics that has been carried out in animals models treated with antidepressants (Malki et al. 2016), but it still lacks meaningful application to humans.

1.4 Complementary Approaches

Genetic polymorphisms represent somehow a first level of biomarker considering that gene expression depends on several regulatory mechanisms and the final protein levels are affected by gene expression level but also by protein metabolism. Thus, there are categories of biomarkers that are complementary to genomic ones, particularly those studied by epigenomics, transcriptomics, and proteomics.

Epigenomics is the study of epigenetic modifications that are reversible modifications on DNA or histones that affect gene expression without altering the DNA sequence. Epigenomic

maintenance is a continuous process that is pivotal for adaptation to the environment and biological mechanisms like DNA repair (Alabert and Groth 2012). Exposure to pharmaceuticals, nutrition, and stress are capable of producing epigenetic modifications with possible lasting effects on human development, metabolism, and health. The most characterized epigenetic modifications are DNA methylation and histone modification, and the former was particularly studied in relation to antidepressant response. The classic type of DNA methylation refers to the addition of a methyl group to the cytosine pyrimidine ring located in CpG dinucleotide sites within genes that affect gene expression. Epigenetic modifications in a number of genes have been linked to childhood trauma and MDD, such as FKBP5 and BDNF, and antidepressants were demonstrated to have epigenetic effects (Lisoway et al. 2017). Studies investigating gene methylation in association with antidepressant response are currently limited in number, and whether increased or decreased DNA methylation is related to response differs across studies and by genetic loci. Other issues are that the most part of studies focused on baseline levels of DNA methylation rather than the reversal of probable pathological epigenetic patterns through effective treatment and almost all studies had a candidate gene approach. Taking into account these limitations, epigenetic modifications of SLC6A4, BDNF, and IL11 genes showed promising results as biomarkers for prediction of antidepressant response (Lisoway et al. 2017).

Transcriptomics is the study of gene expression levels that are usually determined in blood. Blood as a target tissue is easily accessible, and gene expression levels in blood have shown to be comparable with those obtained in prefrontal cortex, thanks to MDD-related transcriptomic research (Lin and Tsai 2016). Candidate gene studies mainly investigated the expression of genes involved in inflammation [interleukin 1 beta (IL-1B), macrophage migration inhibitory factor (MIF), tumor necrosis factor alpha (TNFα)] and neurotrophins [BDNF and nerve growth factor (VGF)], and they reported that these biomarkers may be baseline predictors of treatment outcome or show different variations at follow-up depending on treatment outcome (Fabbri et al. 2016). Several genome-wide gene expression studies have investigated antidepressant response. One of those proposed RORA as peripheral marker of antidepressant response (Lin and Tsai 2016) and interestingly this gene was among the top findings of a previous GWAS (Garriock et al. 2010). The other available transcriptomic studies reported several genes involved in inflammatory processes among significant results, particularly IRF7, IRF2, IL1B, TNF, CD3D, CD97, IFITM3, and GZMA. Two transcriptomics studies investigated also which combination of markers showed the best predictive properties. The first model included the expression of four genes (PPT1, TNF, IL1B, and HIST1H1E) that was reported to predict antidepressant efficacy with area under the ROC curve of 0.94, but no independent replication was carried out. Another 13-genes model was also proposed, including genes associated with immune/inflammatory activation (CD3D, CD97, IFITM3, and GZMA) and mediation of cell proliferation (GZMA and TIMP1). The model showed sensitivity of 66.7 to predict non-remission in the original sample and of 86.1 in an independent sample including six genes of the original set of 13 (Lin and Tsai 2016). These findings are the first attempts to translate transcriptomics in clinical applications for predicting antidepressant response, but clearly they still lack of the required validation and reproducibility and more research is needed.

Fewer studies investigated proteomics biomarkers of antidepressant response, indeed the most part of studies focused on single proteins, particularly neurotrophins [BDNF and glial cell line-derived neurotrophic factor (GDNF)] and inflammatory markers [C reactive protein (CRP), IL-1, IL-6 and TNF-α] (Fabbri et al. 2017).

Conclusion

This chapter summarized the available knowledge in the field of antidepressant pharmacogenetics and pharmacogenomics and provided some information about complementary approaches, in particular epigenomics and transcriptomics.

The existing literature focused on the candidate gene approach for more than a decade, and current clinical applications are based on the results of this type of studies. Candidate gene studies demonstrated that a number of genes involved in antidepressant mechanisms of action (such as BDNF, SLC6A4, HTR2A) and antidepressant pharmacokinetics (CYP450 and ABCB1 genes) are probably modulators of antidepressant efficacy with small individual effect sizes. Despite these results provided useful information about the role of a limited number of genes, the complexity of antidepressant pharmacogenomics cannot be identified by the candidate approach. GWAS have become a quite spread methodology only in the last 7–8 years in psychiatric research, and analysis approaches based on genome-wide data probably still need improvement, as suggested by the recent development of multi-marker tests. The evolution of analysis methods is a pivotal issue for the progress of research in pharmacogenomics since the recent rapid improvement of genotyping technologies that is not limited to GWAS, but it is quickly moving to whole genome sequencing. As reported previously in this chapter, the cost of whole human genome sequencing dropped from 100 million dollars in 2001 to 1000 dollars today, encouraging the creation of national biobanks in a number of countries. As examples, the US Precision Medicine Initiative (https://www.nih.gov/research-training/allofus-research-program) coordinated by the National Institutes of Health (NIH) and the UK Biobank (https://www.ukbiobank.ac.uk/about-biobank-uk/) established by UK Health Government authorities and supported by the National Health Service (NHS). Both projects aim to collect health-related measures through medical health records and biological specimens for biomarkers determination (including genome sequencing) on a large part of the general population (500,000–1 million or more subjects). UK Biobank recruited 500,000 people aged between 40 and 69 years in 2006–2010, and the US Precision Medicine Initiative is going to start recruitment in 2017. These projects are expected to improve the prevention, diagnosis, and treatment of a wide range of serious illness including psychiatric disorders through the development of measures of disease risk, predictors of individual disease evolution, and treatment response. Further desirable outcomes are the improvement of our knowledge in disease pathogenesis and identification of new drug targets.

Figure 1.1 provides a representation of the different methodological approaches to antidepressant pharmacogenetics/pharmacogenomics. The recent acceleration of progress in the field suggests that innovative and more robust findings will be obtained in the near future.

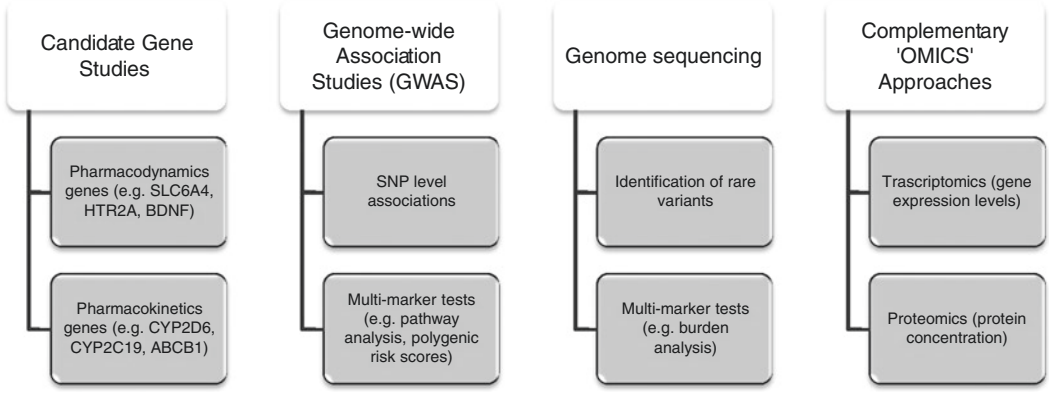

Fig. 1.1 Overview of methodological approaches in the study of antidepressant pharmacogenetics and pharmacogenomics

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